PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference PCT 21058Y	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US03/19393	International filing date *(day/month/year)* 20 June 2003 (20.06.2003)	Priority date *(day/month/year)* 24 June 2002 (24.06.2002)
International Patent Classification (IPC) or national classification and IPC IPC(7): C07C 215/50, 215/52, 215/54; A01N 33/02; A61K 31/135 and US Cl.: 564/355; 514/653		
Applicant MERCK & CO., INC.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 3 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 3 sheets. EPO - DG 1

3. This report contains indications relating to the following items: 17. 12. 2004

   - I ☒ Basis of the report (52)
   - II ☐ Priority
   - III ☐ Non-establishment of report with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
15 December 2003 (15.12.2003)	06 October 2004 (06.10.2004)
Name and mailing address of the IPEA/US Mail Stop PCT, Attn: IPEA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 305-3230	Authorized officer Brian J. Davis Telephone No. 571-272-2717

Form PCT/IPEA/409 (cover sheet)(July 1998)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US03/19393

I. Basis of the report

1. With regard to the elements of the international application:*

☐ the international application as originally filed.

☒ the description:
pages 1-40 as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☒ the claims:
pages 43, 44 and 46-49, as originally filed
pages NONE, as amended (together with any statement) under Article 19
pages NONE, filed with the demand
pages 41,42 and 45, filed with the letter of 12 August 2004 (12:08.2004)

☐ the drawings:
pages NONE, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☐ the sequence listing part of the description:
pages NONE, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination(under Rules 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in printed form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages NONE

☐ the claims, Nos. NONE

☐ the drawings, sheets/~~fig~~ NONE

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*
*** Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US03/19393

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. STATEMENT

Novelty (N)	Claims 1-11	YES
	Claims none	NO
Inventive Step (IS)	Claims 1-11	YES
	Claims none	NO
Industrial Applicability (IA)	Claims 1-11	YES
	Claims NONE	NO

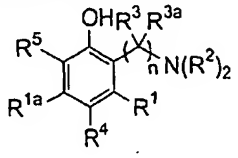
2. CITATIONS AND EXPLANATIONS

Claims 1-11 meet the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest applicant's compounds, compositions and method of treating malaria (see in particular the instant substituent definitions of R^1, R^{1a} and R^5).

Claims 1-11 meet the criteria set out in PCT Article 33(4), and thus have industrial applicability because the subject matter claimed can be made or used in industry.

WHAT IS CLAIMED IS:

1. A compound of formula I:



wherein,

R^5 is hydrogen;

R^{1a} and R^1 independently are C_{1-6} alkyl, halo, C_{1-6} alkoxy, C_{3-10} cycloalkyl, C_{6-10} aryl, and trihalovinyl, said aryl optionally substituted with 1-3 groups of R^a;

R^2 is hydrogen, C_{1-6} alkyl, and C_{3-10} cycloalkyl; taken together with any intervening atoms can form a 3 to 7 membered carbocyclic or heterocyclic ring saturated or unsaturated, said heterocyclic ring containing 1-2 heteroatoms independently chosen from O, C(O), S, SO, SO_2, N, or NR^{2a} and optionally substituted by 1-3 Ra groups;

R^{2a} is hydrogen, and C_{1-6} alkyl;

R^3 and R^{3a} are independently hydrogen, halo, C_{1-6} alkyl, C_{3-10} cycloalkyl, and C_{6-10} aryl, said aryl and alkyl optionally substituted with 1-3 groups of R^a; or

R^3 and R^{3a} taken together with any intervening atoms can form a 3 to 7 membered carbocyclic or heterocyclic ring saturated or unsaturated, said heterocyclic ring containing 1-2 heteroatoms independently chosen from O, C(O), S, SO, SO_2, N, or NR^{2a} and optionally substituted by 1-3 R^a groups;

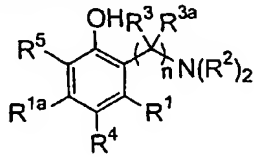
R^4 is hydrogen, halo, C_{1-6} alkyl, and trihaloalkyl;

R^a represents C_{1-6} alkoxy, C_{1-6} alkyl, CF_3, nitro, amino, cyano, C_{1-6} alkylamino, or halogen; and

AMENDED SHEET

WHAT IS CLAIMED IS:

1. A compound of formula I:



wherein,

R^5 is hydrogen;

R^{1a} and R^1 independently are C_{1-6} alkyl, halo, C_{1-6} alkoxy, C_{3-10} cycloalkyl, C_{6-10} aryl, and trihalovinyl, said aryl optionally substituted with 1-3 groups of R^a;

R^2 is hydrogen, C_{1-6} alkyl, and C_{3-10} cycloalkyl; taken together with any intervening atoms can form a 3 to 7 membered carbocyclic or heterocyclic ring saturated or unsaturated, said heterocyclic ring containing 1-2 heteroatoms independently chosen from O, C(O), S, SO, SO_2, N, or NR^{2a} and optionally substituted by 1-3 Ra groups;

R^{2a} is hydrogen, and C_{1-6} alkyl;

R^3 and R^{3a} are independently hydrogen, halo, C_{1-6} alkyl, C_{3-10} cycloalkyl, and C_{6-10} aryl, said aryl and alkyl optionally substituted with 1-3 groups of R^a; or

R^3 and R^{3a} taken together with any intervening atoms can form a 3 to 7 membered carbocyclic or heterocyclic ring saturated or unsaturated, said heterocyclic ring containing 1-2 heteroatoms independently chosen from O, C(O), S, SO, SO_2, N, or NR^{2a} and optionally substituted by 1-3 R^a groups;

R^4 is hydrogen, halo, C_{1-6} alkyl, and trihaloalkyl;

R^a represents C_{1-6} alkoxy, C_{1-6} alkyl, CF_3, nitro, amino, cyano, C_{1-6} alkylamino, or halogen; and

n represents 1-3;

or a pharmaceutically acceptable salt, enantiomer, or diasteriomer thereof.

2. A compound according to claim 1 wherein R^{1a} and R^1 independently are tert-butyl, 1,2,2-trichlorovinyl, or phenyl .

3. A compound according to claim 1 wherein R^2 is hydrogen or C_{1-4} alkyl, and n is 1.

4. A compound according to claim 1 wherein R^{1a} and R^1 independently are tert-butyl, 1,2,2-trichlorovinyl, or phenyl; R^2 is hydrogen or C_{1-4} alkyl, and n is 1.

5. A compound according to claim 4 wherein R^{1a} and R^1 are tert-butyl, and R^2 is hydrogen.

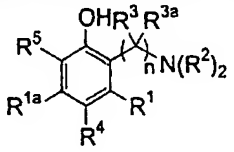
6. A compound which is:
2-aminomethyl-5-tert-butyl-3-phenylphenol,
2-aminomethyl-5-tert-butyl-3-(4-methylphenyl)phenol,
3,5-di-tert-butyl-2-[(ethylamino)methyl]phenol,
3,5-di-tert-butyl-2-[1-(ethylamino)ethyl]phenol,
3,5-di-tert-butyl-2-[(methylamino)methyl]phenol,
3,5-bis(trichlorovinyl)-2-[(ethylamino)methyl]phenol,
3,5-di-tert-butyl-2-[(propylamino)methyl]phenol,
2-[(ethylamino)methyl]-5-(trichlorovinyl)phenol,
3,5-di-tert-butyl-2-[(butylamino)methyl]phenol,
3,5-di-tert-butyl-2-[(cyclohexylamino)methyl]phenol,
3,5-di-tert-butyl-2-[(hexylamino)methyl]phenol,
3,5-di-tert-butyl-2-[(octylamino)methyl]phenol,
3,5-di-tert-butyl-2-[(2-hydroxyethylamino)methyl]phenol,
tert-butyl N-(2,4-di-tert-butyl-6-hydroxybenzyl)-beta-alaninate,
3,5-di-tert-butyl-2-[(2-dimethylaminoethylamino)methyl]phenol,
3,5-di-tert-butyl-2-[(3-phenylpropylamino)methyl]phenol,

2-(1-Aminoethyl)-3,5-di-*tert*-butylphenol,
3,5-Di-*tert*-butyl-2-[1-(ethylamino)ethyl]phenol,
3,5-Di-*tert*-butyl-2-[(propylamino)methyl]phenol,
3,5-Di-*tert*-butyl-2-{[(pyrazin-2-ylmethyll)amino]methyl}phenol,
2-(aminomethyl)-3,5-di-*tert*-butylphenol hydrochloride,
2-Aminomethyl-5-*tert*-butylphenol hydrochloride,
or pharmaceutically acceptable salts thereof.

7. A composition comprising a compound of claim 1 and a pharmaceutically acceptable salt thereof.

8. A composition comprising a compound of claim 6 and a pharmaceutically acceptable salt thereof.

9. A method for the treatment of malaria which comprises administering to a patient in need of such treatment a compound of formula I:



wherein,

R^5 is hydrogen;

R^{1a} and R^1 independently are C_{1-6} alkyl, halo, C_{1-6} alkoxy, C_{3-10} cycloalkyl, C_{6-10} aryl, and trihalovinyl, said aryl optionally substituted with 1-3 groups of R^a;

R^2 is hydrogen, C_{1-6} alkyl, and C_{3-10} cycloalkyl; taken together with any intervening atoms can form a 3 to 7 membered carbocyclic or heterocyclic ring saturated or unsaturated, said heterocyclic ring containing 1-2 heteroatoms independently chosen from O, C(O), S, SO, SO_2, N, or NR2a and optionally substituted by 1-3 Ra groups;